

Validation of a prognostic scoring system for postmastectomy locoregional recurrence in breast cancer[☆]

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ARTICLE INFO

Keywords:

Breast cancer
Radiotherapy
Mastectomy
Locoregional recurrence
Prognostic scoring system

ABSTRACT

Background: To date, it remains unclear which patients with breast cancer (BC) benefit from post-mastectomy radiotherapy (PMRT). Cheng et al. developed and validated a scoring system based on 4 prognostic factors for locoregional recurrence (LRR) to identify patients in need for PMRT. These factors include age, estrogen receptor status, lymphovascular status and number of affected axillary lymph nodes.

Purpose: To validate the scoring system for LRR in BC developed by Cheng et al. by using an independent BC database.

Methods and materials: We retrospectively identified 1989 BC cases, treated with mastectomy (ME) with or without PMRT at the University Hospitals Leuven between 2000 and 2007. The primary endpoint was 5-year locoregional control rate with and without PMRT, according to the LRR score.

Results: Median follow-up time was 11.4 years. After excluding patients with missing variables 1103 patients were classified using the LRR scoring system: 688 (62.38%) patients were at low risk of recurrence (LRR score 0–1), 335 (30.37%) patients were at intermediate risk of recurrence (LRR score 2–3) and 80 (7.25%) patients were at high risk of recurrence (LRR score ≥ 4). 5-year locoregional control rates with and without PMRT were 99.20% versus 99.21% ($p = 0.43$) in the low-risk group; 98.24% versus 85.74% ($p < 0.0001$) in the intermediate-risk group and 96.87% versus 85.71% ($p = 0.10$) in the high-risk group respectively.

Conclusion: Our validation of the LRR scoring system suggests it can be used to point out patients that would benefit from PMRT. We recommend further validation of this scoring system by other independent institutions before application in clinical practice.

1. Introduction

Breast cancer (BC) continues to be the most common malignancy and the main cause of cancer death among women worldwide; although in Europe, BC mortality continues to decline [1,2]. With the current treatment options in the Western world BC already has a relatively good prognosis, therefore one of the remaining challenges in the treatment of BC is to move towards a more personalized approach where strategies of

de-escalation need to be explored to avoid side-effects [3]. On the other hand subgroups of patients in need of extensive treatment need to be defined more specifically. One of these remaining issues in the treatment of BC is defining selection criteria for patients to undergo post-mastectomy radiotherapy (PMRT). In this matter, current international guidelines state that PMRT is recommended for high-risk patients only, including involved resection margins, at least four involved axillary lymph nodes (LN), and T3-T4 tumours independent of the nodal

Abbreviations: BC, breast cancer; CT, chemotherapy; ECE, extracapsular extension; ER, estrogen receptor; HT, hormonal therapy; LN, lymph nodes; LRC, locoregional control; LRR, locoregional recurrence; LVI, lymphovascular invasion; ME, mastectomy; PMRT, post-mastectomy radiotherapy; RT, radiotherapy.

[☆] Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

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<https://doi.org/10.1016/j.breast.2022.04.007>

Received 13 February 2022; Received in revised form 26 March 2022; Accepted 13 April 2022

Available online 18 April 2022

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status [4]. Nevertheless, several more recent studies suggest we should also consider the use of PMRT in intermediate-risk patients with 1–3 positive axillary LN [5,6].

To date, guidelines and nomograms help us in the clinical decision-making to personalize the treatment of BC. In this respect, the group of Cheng et al. developed a clinical prognostic scoring system in 2006 for 5-year locoregional recurrence (LRR) based on 1010 BC patients treated between 1990 and 2001 to identify patients most in need of PMRT. This scoring system incorporated four risk factors for LRR: young age, lymphovascular invasion (LVI), estrogen receptor (ER) negativity, and the number of involved axillary LN [7]. The scoring system is presented in Table 1.

This model has been tested and adjusted by the group of Cheng after examining a new dataset of 1545 patients treated between 2002 and 2007 [8]. To conclude, Cheng et al. recommends PMRT in 1–3 node-positive patients with a LRR score of 2 or more [8].

To apply a prognostic scoring model in clinical use it needs to be evaluated, adjusted and finally validated in different independent cohort analyses. The TRIPOD statement defines this as a type 4 modelling strategy, which is the most reliable way to validate a prognostic scoring system [9]. Therefore, the aim of this study is to validate the prognostic scoring system for LRR in BC developed by Cheng et al. by using a large, external and independent cancer database of patients with BC treated between 2000 and 2007.

2. Material and methods

2.1. Study design

This study consists of the validation of a previously developed LRR scoring system by Cheng et al. by using retrospectively collected data from an independent cancer database [7,8].

2.2. Scoring system by Cheng et al

The scoring system is presented in Table 1.

In this scoring system patients receive a score from 0 to 6, thereby dividing all patients into 3 subgroups: a low-risk group (LRR score 0–1), an intermediate-risk group (LRR score 2–3) and a high-risk group (LRR score ≥4). The different risk factors account for different scores: age ≤40, prominent LVI, ER negativity and 1–3 positive axillary LN all have a prognostic score of 1. The presence of 4–9 positive axillary LN has a prognostic score of 2 and the presence of 10 or more positive axillary LN has a prognostic score of 3. The LRR score is obtained by summing up the values of each risk factor that is present, leading to a score of at least 0 to a maximal score of 6 for each patient.

Table 1
LRR scoring system by Cheng et al.

| Risk factor | Presence | Prognostic score |
|-------------------------------|-------------|--------------------|
| Age | >40 years | 0 |
| | ≤40 years | 1 |
| Lymphovascular Invasion | Not present | 0 |
| | Present | 1 |
| Estrogen Receptor Status | Positive | 0 |
| | Negative | 1 |
| Positive Axillary Lymph Nodes | None | 0 |
| | 1–3 | 1 |
| | 4–9 | 2 |
| | ≥10 | 3 |
| LRR score | | Total score |
| Low Risk | | 0–1 |
| Intermediate Risk | | 2–3 |
| High Risk | | ≥4 |

2.3. Patient selection and data collection

Patients who underwent ME between 2000 and 2007 for primary invasive BC of which at least ME and/or PMRT had to be performed at the University Hospitals Leuven were included. Exclusion criteria included (i) male sex; (ii) distant metastasis at diagnosis, (iii) bilateral invasive BC at diagnosis and (iv) neo-adjuvant chemotherapy (CT), (v) neo-adjuvant hormonal therapy (HT) or (vi) neo-adjuvant radiotherapy (RT).

The Ethical committee of the University Hospitals Leuven accepted this study.

2.4. Locoregional recurrence

Time until LRR was determined as the time from the first day of treatment until the day of chest wall or regional nodal recurrence.

2.5. Statistical analysis

This analysis was performed in analogy with Cheng et al. [7]. However, given the unequal times of follow-up, analysing LRR as a binary variable was not indicated. LRR was therefore analysed as a time-to-event variable. Cox proportional hazards models were used to analyse the association between potential risk factors and locoregional control (LRC) (LRR as a time-to-event variable). The multivariable model included the same variables as in Cheng et al. The Kaplan-Meier method was used to estimate 5-y LRC. The log-rank test was used to compare local control between groups. Finally, in analogy with the validation of Cheng et al. the influence of PMRT on the 5-year LRC rate was analysed by subgroup analyses with tumour size, multicentricity and the LRR score as defining factors. Analyses have been performed using SAS software (version 9.4 of the SAS System for Windows).

3. Results

3.1. Patient selection

We retrospectively identified 1989 BC cases, treated with ME of which either PMRT and/or ME were performed at the University Hospitals Leuven from 2000 until 2007. 32 male patients were excluded from analysis, followed by exclusion of 14 patients with distant metastasis at diagnosis; 106 patients with concurrent bilateral invasive BC and 211 and 40 patients whom received neo-adjuvant CT or neo-adjuvant HT respectively.

1586 patients remained eligible for analysis (Fig. 1).

3.2. Patient characteristics

An overview of patient characteristics is presented in Table 2.

According to the LRR scoring system 62.38% of patients were at low risk of recurrence (LRR score 0–1); 30.37% of patients were at intermediate risk of recurrence (LRR score 2–3) and 7.25% patients were at high risk of recurrence (LRR score 4 or more). In each group the majority of patients received adjuvant RT; in particular 58.43% of patients in the low-risk group, 88.96% of patients in the intermediate-risk group and 90.00% of patients in the high-risk group.

Median follow-up time was 11.4 years (range 0.0–18.7 years).

3.3. Locoregional recurrence

At the time of data collection only 46 (2.90%) patients had relapsed with a LRR.

Table 3 shows the univariable and multivariable analysis of prognostic factors for LRR analysed by Cox proportional hazards regression modelling. Significant risk factors for LRR on univariable analysis include nuclear grade 3 (HR 2.3, 95% CI 1.2–4.3), LVI (HR 4.0, 95% CI

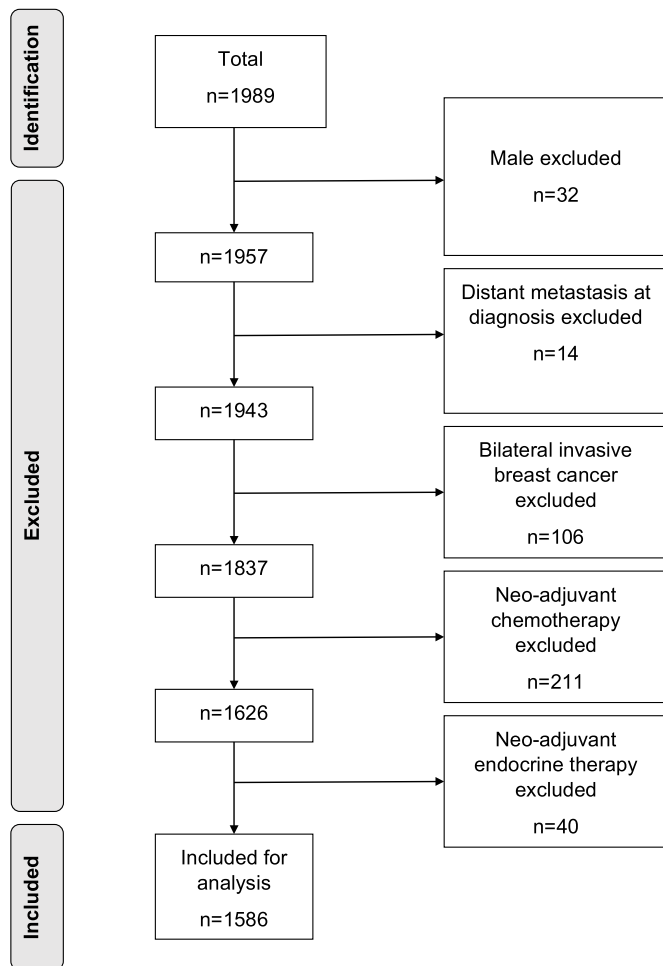


Fig. 1. Flow diagram of the patient selection process.

2.0–8.1), a LRR score of 2–3 (HR 2.4, 95% CI 1.2–5.1) and a LRR score of 4 or more (HR 3.4, 95% CI 1.1–10.3). The multivariable model includes the predictors from the multivariable model reported by Cheng et al. and shows that the LRR score is the most significant independent prognostic risk factor for predicting LRR. A LRR score of 2–3 has a HR of 4.1 (95% CI 1.8–9.6) and a LRR score of 4 or more has a HR of 6.4 (95% CI 1.9–22.1). Furthermore, multivariable analysis shows adjuvant RT is a significant independent factor for reducing LRR with a HR of 0.3 (95% CI 0.1–0.7).

3.4. LRC and the influence of PMRT

Table 4 demonstrates the influence of PMRT on LRC for different LRR scores and according to the nodal status. 1103 patients were classified according to the LRR scoring system developed by Cheng et al. of which 688 (62.38%) patients were at low risk of recurrence (LRR score 0–1), 335 (30.37%) patients were at intermediate risk of recurrence (LRR score 2–3) and 80 (7.25%) patients were at high risk of recurrence (LRR score ≥ 4). Of these the 5-year LRC rates with and without PMRT were 99.20% versus 99.21% ($p = 0.43$) in the low-risk group; 98.24% versus 85.74% ($p < 0.0001$) in the intermediate-risk group and 96.87% versus 85.71% ($p = 0.10$) in the high-risk group respectively. Furthermore Table 4 also shows the effect of PMRT on LRC for node negative and node positive patients separately. For the node negative patients in the low-risk group, no difference was found in the 5-year LRC rates with and without PMRT ($p = 0.3628$). However, even with a small number of 29 patients in the node negative intermediate risk group a remarkably statistically significant LRC rate difference was found of 100.00% versus

Table 2

Clinical characteristics of patients in this validation cohort.

| Characteristics | Patient no. |
|-------------------------------|----------------------------|
| Age | |
| ≤35 | n/N (%) 51/1586 (3.22%) |
| 36–40 | n/N (%) 86/1586 (5.42%) |
| 41–50 | n/N (%) 379/1586 (23.90%) |
| 51–60 | n/N (%) 419/1586 (26.42%) |
| >60 | n/N (%) 651/1586 (41.05%) |
| Menstruation status | |
| Premenopausal | n/N (%) 566/1549 (36.54%) |
| Postmenopausal | n/N (%) 983/1549 (63.46%) |
| Missing data | n 37 |
| Histology | |
| Favorable ^a | n/N (%) 48/1584 (3.03%) |
| Infiltrating ductal | n/N (%) 1136/1584 (71.72%) |
| Other invasive | n/N (%) 326/1584 (20.58%) |
| Mixed type | n/N (%) 74/1584 (4.67%) |
| Missing data | n 2 |
| Axillary LN surgery | |
| Sentinel LN biopsy only | n/N (%) 61/1586 (3.85%) |
| Axillary LN dissection | n/N (%) 1518/1586 (95.71%) |
| No axillary LN surgery | n/N (%) 7/1586 (0.44%) |
| Pathological tumour size (cm) | |
| ≤2.0 | n/N (%) 481/1559 (30.85%) |
| >2.0 | n/N (%) 1078/1559 (69.15%) |
| Missing data | n 27 |
| LN positive | |
| 0 | n/N (%) 781/1578 (49.49%) |
| 1–3 | n/N (%) 519/1578 (32.89%) |
| 4–9 | n/N (%) 183/1578 (11.60%) |
| ≥10 | n/N (%) 95/1578 (6.02%) |
| Missing data | n 8 |
| Pathology stage | |
| I | n/N (%) 349/1573 (22.19%) |
| II | n/N (%) 819/1573 (52.07%) |
| III | n/N (%) 405/1573 (25.75%) |
| Missing data | n 13 |
| Estrogen receptor | |
| Negative | n/N (%) 317/1576 (20.11%) |
| Positive | n/N (%) 1259/1576 (79.89%) |
| Missing data | n 10 |
| Progesterone receptor | |
| Negative | n/N (%) 503/1571 (32.02%) |
| Positive | n/N (%) 1068/1571 (67.98%) |
| Missing data | n 15 |
| LVI | |
| Absent | n/N (%) 787/1108 (71.03%) |
| Present | n/N (%) 321/1108 (28.97%) |
| Missing data | n 478 |
| Nuclear grade | |
| Grade 1 | n/N (%) 134/1565 (8.56%) |
| Grade 2 | n/N (%) 698/1565 (44.60%) |
| Grade 3 | n/N (%) 733/1565 (46.84%) |
| Missing data | n 21 |
| HER2/Neu | |
| Negative | n/N (%) 1268/1525 (83.15%) |
| Positive | n/N (%) 257/1525 (16.85%) |
| Missing data | n 61 |
| Multiple foci or centers | |
| Absent | n/N (%) 1279/1579 (81.00%) |
| Present | n/N (%) 300/1579 (19.00%) |
| Missing data | n 7 |
| ECE of axillary LN | |
| LN (–) | n/N (%) 781/1515 (51.55%) |
| LN (+) ECE (–) | n/N (%) 330/1515 (21.78%) |
| LN (–) ECE (+) | n/N (%) 404/1515 (26.67%) |
| Missing data | n 71 |
| Adjuvant radiation therapy | |
| No | n/N (%) 519/1586 (32.72%) |
| Yes | n/N (%) 1067/1586 (67.28%) |
| Adjuvant hormonal therapy | |
| No | n/N (%) 357/1586 (22.51%) |
| Yes | n/N (%) 1229/1586 (77.49%) |
| Adjuvant chemotherapy | |
| No | n/N (%) 842/1586 (53.09%) |
| Yes | n/N (%) 744/1586 (46.91%) |

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Table 2 (continued)

| Characteristics | Patient no. |
|-----------------|---------------------------|
| LRR score | |
| 0–1 | n/N (%) 688/1103 (62.38%) |
| 2–3 | n/N (%) 335/1103 (30.37%) |
| ≥4 | n/N (%) 80/1103 (7.25%) |
| Missing data | n 483 |

Abbreviations: ECE = extracapsular extension; LN = lymph node; LRR = locoregional recurrence; LVI = lymphovascular invasion.

^a Favorable includes medullary, tubular and mucinous carcinomas.

76.92% (p = 0.045). There were no high-risk patients in the node negative group. For the node positive patients an additional difference was made between 1 - 3 node positive patients and 4 or more node positive patients. In the 1 to 3 node positive group 206 patients were found to be at low risk of recurrence, all having a 100.00% 5-year LRC rate with or without PMRT (p = 0.63). In the intermediate-risk group 5-year LRC rates were superior in the PMRT group than in the group without PMRT (97.55% versus 87.50% respectively, p = 0.01). In the high-risk group all 4 patients underwent PMRT so no comparison of 5-year LRC with or without PMRT could be made. For the patients with 4 or more positive axillary LN the 5-year LRC rates with and without PMRT were 97.55% versus 87.50% (p = 0.01) in the-intermediate risk group and 96.87% versus 85.71% (p = 0.10) in the high-risk group. No patients with 4 or more positive axillary LN were found to be at low risk.

3.5. Other prognostic factors

Table 5 shows the influence of PMRT on the 5-year LRC rate when tumour size and multicentricity are added to the LRR score as additional factors. For patients at low risk of recurrence (LRR score 0–1) there was no significant influence of primary tumour size nor multicentricity or PMRT on the 5-year LRC rate. For patients at intermediate risk (LRR score 2–3) with a tumour size > 2 cm or multicentricity on the other hand, the use of PMRT showed significantly improved 5-year LRC rates versus no PMRT (98.04% versus 84.25% respectively, p < 0.0001). Intermediate-risk patients without primary tumour size > 2 cm nor multicentricity had a 5-year LRC rate of 100.00% with PMRT versus 90.00% without PMRT (p = 0.07). When patients at intermediate risk have 0 to 3 positive axillary LN and a primary tumour size > 2 cm or multicentricity PMRT also leads to a superior 5-year LRC versus no PMRT in this group (97.40% versus 80.00% respectively, p < 0.0001). When these patients do not have primary tumour size > 2 cm nor multicentricity, PMRT does not lead to statistically significant better 5-year LRC rates than no PMRT (100.00% versus 88.89% respectively, p = 0.43). For patients at high risk of recurrence (score ≥4) with a primary tumour size > 2 cm or multicentricity our validation could not demonstrate a statistically significant benefit from PMRT at 5-year LRC (98.31% PMRT versus 85.71%, p = 0.05).

4. Discussion

Despite years of investigation selection of patients to undergo PMRT remains controversial. Initially, international guidelines stated that PMRT was recommended for high-risk patients only, including involved resection margins, at least four involved axillary LN and T3-T4 tumours independent of the nodal status [4]. Nevertheless, several more recent studies suggest we should also consider the routine use of PMRT in intermediate-risk patients with 1–3 positive axillary LN with the exception of axillary micrometastasis and isolated tumour cells [5,6,10]. Until now several studies have investigated this matter with conflicting results. On the one hand, the Early Breast Cancer Trialists' Collaborative Group for instance demonstrated a 10% 10-year risk reduction of any recurrence (locoregional and distant), as well as an 8% 20-year risk reduction of BC-related mortality with PMRT in node-positive patients

Table 3

Factors associated with 5-y LRR by univariable and multivariable analyses.

| Variables | Patient no. n/N (%) | Univariable analysis | | Multivariable analysis | |
|----------------------------|---------------------|------------------------------|---------|------------------------------|---------|
| | | Hazard ratio of LRR (95% CI) | P value | Hazard ratio of LRR (95% CI) | P value |
| Age at diagnosis | | | | | |
| >40 | 1449/1586 (91.36%) | 1 | | | |
| ≤40 | 137/1586 (8.64%) | 1.74 (0.78; 3.89) | 0.18 | | |
| Tumour size (cm) | | | | | |
| ≤2.0 | 481/1559 (30.85%) | 1 | | 1 | |
| >2.0 | 1078/1559 (69.15%) | 1.04 (0.55; 1.95) | 0.91 | 0.84 (0.37; 1.85) | 0.64 |
| LN positive | | | | | |
| 0 | 781/1578 (49.49%) | 1 | | | |
| 1–3 | 519/1578 (32.89%) | 1.04 (0.53; 2.05) | 0.90 | | |
| ≥4 | 278/1578 (17.62%) | 1.41 (0.65; 3.09) | 0.38 | | |
| Estrogen receptor | | | | | |
| Positive | 1259/1576 (79.89%) | 1 | | | |
| Negative | 317/1576 (20.11%) | 1.57 (0.81; 3.04) | 0.18 | | |
| HER2 | | | | | |
| Negative | 1268/1525 (83.15%) | 1 | | | |
| Positive | 257/1525 (16.85%) | 0.98 (0.44; 2.21) | 0.97 | | |
| Nuclear grade | | | | | |
| I-II | 832/1565 (53.16%) | 1 | | | |
| III | 733/1565 (46.84%) | 2.32 (1.24; 4.35) | 0.01 | | |
| LVI | | | | | |
| Absent | 787/1108 (71.03%) | 1 | | | |
| Present | 321/1108 (28.97%) | 4.02 (2.00; 8.08) | <0.0001 | | |
| Multicentricity | | | | | |
| Absent | 1279/1579 (81.00%) | 1 | | 1 | |
| Present | 300/1579 (19.00%) | 1.59 (0.82; 3.09) | 0.17 | 1.81 (0.79; 4.12) | 0.16 |
| ECE | | | | | |
| Absent | 1111/1515 (73.33%) | 1 | | | |
| Present | 404/1515 (26.67%) | 1.05 (0.51; 2.15) | 0.90 | | |
| LRR score | | | | | |
| Score 0-1 | 688/1103 (62.38%) | 1 | | 1 | |
| Score 2-3 | 335/1103 (30.37%) | 2.43 (1.15; 5.10) | 0.02 | 4.14 (1.79; 9.61) | <0.01 |
| Score ≥4 | 80/1103 (7.25%) | 3.36 (1.09; 10.30) | 0.03 | 6.43 (1.87; 22.08) | <0.01 |
| Adjuvant radiation therapy | | | | | |
| No | 519/1586 (32.72%) | 1 | | 1 | |
| Yes | 1067/1586 (67.28%) | 0.59 (0.33; 1.05) | 0.07 | 0.32 (0.14; 0.74) | 0.01 |
| Adjuvant hormonal therapy | | | | | |
| No | 357/1586 (22.51%) | 1 | | | |
| Yes | | | 0.06 | | |

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Table 3 (continued)

| Variables | Patient no. n/N (%) | Univariable analysis | | Multivariable analysis | |
|-----------------------|---------------------|------------------------------|---------|------------------------------|---------|
| | | Hazard ratio of LRR (95% CI) | P value | Hazard ratio of LRR (95% CI) | P value |
| | 1229/1586 (77.49%) | 0.56 (0.30; 1.03) | | | |
| Adjuvant chemotherapy | | | | | |
| No | 842/1586 (53.09%) | 1 | | | |
| Yes | 744/1586 (46.91%) | 1.04 (0.58; 1.85) | 0.90 | | |

Table 4

LRC versus LRR score and nodal status.

| Risk group | Radiation therapy | Patient no. n/N (%) | 5-y LRC (%) | P value |
|------------------------------|-------------------|---------------------|-------------|---------|
| All patients | | | | |
| LRR score 0-1 | Yes | 402/772 (52.07%) | 99.20% | 0.43 |
| | No | 286/331 (86.40%) | 99.21% | |
| LRR score 2-3 | Yes | 298/772 (38.60%) | 98.24% | <0.0001 |
| | No | 37/331 (11.18%) | 85.74% | |
| LRR score ≥4 | Yes | 72/772 (9.33%) | 96.87% | 0.10 |
| | No | 8/331 (2.42%) | 85.71% | |
| Node (-) patients | | | | |
| LRR score 0-1 | Yes | 223/239 (93.31%) | 98.55% | 0.36 |
| | No | 259/272 (95.22%) | 99.15% | |
| LRR score 2-3 | Yes | 16/239 (6.69%) | 100.00% | 0.045 |
| | No | 13/272 (4.78%) | 76.92% | |
| Node 1–3 (+) patients | | | | |
| LRR score 0-1 | Yes | 179/354 (50.56%) | 100.00% | 0.63 |
| | No | 27/44 (61.36%) | 100.00% | |
| LRR score 2-3 | Yes | 171/354 (48.31%) | 97.55% | 0.01 |
| | No | 17/44 (38.64%) | 87.50% | |
| LRR score ≥4 | Yes | 4/354 (1.13%) | – | – |
| | No | 0/44 (0.00%) | – | |
| Node ≥4 (+) patients | | | | |
| LRR score 2-3 | Yes | 111/179 (62.01%) | 97.55% | 0.01 |
| | No | 7/15 (46.67%) | 87.50% | |
| LRR score ≥4 | Yes | 68/179 (37.99%) | 96.87% | 0.10 |
| | No | 8/15 (53.33%) | 85.71% | |

Abbreviations: LRC = locoregional control; LRR = locoregional recurrence.

[5]. Additionally they demonstrated that the benefits of PMRT are independent from the number of involved axillary LN. On the other hand some other recent studies question the advantages of PMRT. The breast international group (BIG 02.98 trial) for example confirmed LRC improved with PMRT in 1–3 node positive patients, but did not confirm superior BC specific nor overall survival with PMRT [11]. Another study showed similar results, with no significant overall survival with PMRT in patients with T1-T2 N1 disease [12]. As a result of these controversial findings some studies even discourage using nodal cut-off as an indicator for adjuvant therapy, because they could not demonstrate a prognostic cut-off in the number of involved LN to differ between a low and a high-risk group [13].

In this respect many research has been conducted in an attempt to identify prognostic factors that indicate those patients that benefit the most from PMRT [14–21]. Besides nodal stage, risk factors identified were young age, tumour size, ECE, ER negative status, triple negative breast cancer, histologic grade, lymph node ratio (ratio of the number of

Table 5

Incorporating other risk factors into the LRR score.

| Risk group | T > 2 cm or multiple | Radiation therapy | Patient no. n/N (%) | 5-y LRC (%) | P value |
|------------------------------|----------------------|-------------------|---------------------|-------------|---------|
| LRR score 0-1 | Yes | Yes | 346/401 (86.28%) | 99.37% | 0.79 |
| | | No | 168/284 (59.15%) | 98.60% | |
| | No | Yes | 55/401 (13.72%) | 98.11% | 0.58 |
| | | No | 116/284 (40.85%) | 100.00% | |
| LRR score 2-3 | Yes | Yes | 268/297 (90.24%) | 98.04% | <0.0001 |
| | | No | 27/37 (72.97%) | 84.25% | |
| | No | Yes | 29/297 (9.76%) | 100.00% | 0.07 |
| | | No | 10/37 (27.03%) | 90.00% | |
| LRR score 2-3 and LN (+) < 4 | Yes | Yes | 161/186 (86.56%) | 97.40% | <0.0001 |
| | | No | 21/30 (70.00%) | 80.00% | |
| | No | Yes | 25/186 (13.44%) | 100.00% | 0.43 |
| | | No | 9/30 (30.00%) | 88.89% | |
| LRR score ≥4 | Yes | Yes | 65/72 (90.28%) | 98.31% | 0.05 |
| | | No | 8/8 (100.00%) | 85.71% | |
| | No | Yes | 7/72 (9.72%) | – | – |
| | | No | 0/8 (0.00%) | – | |

metastatic lymph nodes to the number of removed lymph nodes), a preoperative high neutrophil-to-lymphocyte ratio and a low neutrophil-to-monocyte ratio. The SUPREMO trial (BIG 2.04) is a current on-going trial that determines the overall survival of women at intermediate risk for LRR of BC treated with adjuvant ipsilateral chest wall RT after ME [22]. The results of this study are awaited. To date, guidelines and nomograms help us in the clinical decision-making of PMRT. The scoring system developed by Cheng et al. validated in this study, incorporates four risk factors: young age, LVI, ER negativity, and the number of involved axillary LN [7].

The aim of our study was to validate this scoring system developed by Cheng et al. From our data we can conclude patients in the low-risk group (LRR score 0–1) have good local control with or without PMRT. In the intermediate-risk group (LRR score 2–3) all patients benefit significantly from PMRT with an improved 5-year LRC rate. For patients at high risk of recurrence (LRR score ≥4) our data show a trend towards improved 5-year LRC rates with PMRT, although this tendency is not found to be statistically significant perhaps because numbers in this subgroup were too small to draw conclusions from.

Therefore, we would recommend to spare patients at low risk of recurrence (LRR score 0–1) from PMRT, in this manner avoiding unnecessary side-effects of breast irradiation without compromising 5-year LRC. On the other hand, we would recommend adding PMRT to the treatment of patients at intermediate and high risk of recurrence (LRR score 2 or more) because our data show significantly better 5 year LRC rates with PMRT in the intermediate-risk group versus no PMRT, as well as a tendency towards significant better 5 year LRC in the high-risk group with PMRT versus no PMRT.

There are of course several limitations to our study. Mostly the retrospective design leading to several missing data, as well as the sometimes small numbers in specific subgroups and a low event rate with a total of 46 patients with a LRR perhaps leading to statistically insignificant results in some subgroups. Furthermore, the increasing role of neoadjuvant systemic treatment in BC care was not represented in our

study due to the exclusion of patients treated with neoadjuvant chemotherapy and hormonal therapy from analysis. Consequently, the efficiency of the LRR scoring model in this subgroup of patients remains to be determined.

We expect that in the future the selection of patients to undergo PMRT will be increasingly based on biological and molecular profiling of the tumour cells. Several studies already investigated this matter, with potential aid of genetic profiling (e.g., Oncotype-DX) and the tumour response to preoperative chemotherapy in decision making for PMRT [23–26].

5. Conclusion

To conclude, our validation of the LRR scoring system by Cheng et al. suggests it can be used to point out patients that would benefit from PMRT. We recommend further validation of this scoring system by other independent institutions before application in clinical practice.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of competing interest

None.

Acknowledgements

The authors are grateful for the contribution of Chantal Remmerie to the data search.

References

- Torre LA, Islami F, Siegel RL, Ward EM, Jemal A, et al. Global cancer in women: Burden and trends. *Cancer Epidemiol Biomarkers Prev* 2017 Apr;26(4):444–57.
- Carioli G, Malvezzi M, Rodriguez T, Bertuccio P, Negri E, La Vecchia C. Trends and predictions to 2020 in breast cancer mortality in Europe. *Breast* 2017 Dec;36:89–95.
- Allemani C, Minicozzi P, Berrino F, et al. Predictions of survival up to 10 years after diagnosis for European women with breast cancer in 2000–2002. *Int J Cancer* 2013;132:2404–12.
- Senkus E, Kyriakides S, Ohno S, Penault-Llorca F, Poortmans P, Rutgers E, et al. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2015 Sep;26(Suppl 5):v8–30.
- EBCTCG (Early Breast Cancer Trialists' Collaborative Group), McGale P, Taylor C, Correa C, Cutter D, Duane F, et al. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. *Lancet* 2014 Jun 21;383(9935):2127–35.
- Shi Wenjie, Luo Youhong, Zhao Dongkang, Huang Hao, Pang Weiyi. Evaluation of the benefit of post-mastectomy radiotherapy in patients with early-stage breast cancer: a propensity score matching study. *Oncol Lett* 2019 Jun;17(6):4851–8.
- Cheng SH, Horng CF, Clarke JL, Tsou MH, Tsai SY, Chen CM, et al. Prognostic index score and clinical prediction model of local regional recurrence after mastectomy in breast cancer patients. *Int J Radiat Oncol Biol Phys* 2006 Apr 1;64(5):1401–9.
- Cheng SH, Tsai SY, Yu BL, Horng CF, Chen CM, Jian JJ, et al. Validating a prognostic scoring system for postmastectomy locoregional recurrence in breast cancer. *Int J Radiat Oncol Biol Phys* 2013 Mar 15;85(4):953–8.
- Zwanenburg A, Löck S. Why validation of prognostic models matters? *Radiother Oncol* 2018 Jun;127(3):370–3.
- Mamtani Anita, Patil Sujata, Stempel Michelle, Morrow Monica. Axillary micrometastases and isolated tumor cells are not an indication for post-mastectomy radiotherapy in stage 1 and 2 breast cancer. *Ann Surg Oncol* 2017 Aug;24(8):2182–8.
- Zeidan YH, Habib JG, Ameje L, Paesmans M, de Azambuja E, Gelber RD, et al. Postmastectomy radiation therapy in women with T1-T2 tumors and 1 to 3 positive lymph nodes: analysis of the breast international group 02-98 trial. *Int J Radiat Oncol Biol Phys* 2018 Jun 1;101(2):316–24.
- Abdel-Rahman O. Impact of postmastectomy radiotherapy on the outcomes of breast cancer patients with T1-2 N1 disease : an individual patient data analysis of three clinical trials. *Strahlenther Onkol* 2019 Apr;195(4):297–305.
- Vinh-Hung V1, Storme G. No nodal cutoff in node-positive breast cancer women treated with mastectomy. *Breast Cancer Res Treat* 2006 Jul;98(2):173–8.
- Woodward WA, Strom EA, Tucker SL, Katz A, McNeese MD, Perkins GH, et al. Locoregional recurrence after doxorubicin-based chemotherapy and postmastectomy: implications for breast cancer patients with early-stage disease and predictors for recurrence after postmastectomy radiation. *Int J Radiat Oncol Biol Phys* 2003 Oct 1;57(2):336–44.
- Truong PT, Olivetto IA, Kader HA, Panades M, Speers CH, Berthelet E. Selecting breast cancer patients with T1-T2 tumors and one to three positive axillary nodes at high postmastectomy locoregional recurrence risk for adjuvant radiotherapy. *Int J Radiat Oncol Biol Phys* 2005 Apr 1;61(5):1337–47.
- Gruber G, Cole BF, Castiglione-Gertsch M, Holmberg SB, Lindtner J, Golouh R, et al. Extracapsular tumor spread and the risk of local, axillary and supraclavicular recurrence in node-positive, premenopausal patients with breast cancer. *Ann Oncol* 2008 Aug;19(8):1393–401.
- Duraker Nüvit, Demir Davut, Bati Bakir, Dönmez Yılmaz Binnur, Bati Yasemin, Civelek Çaynak Zeynep, et al. Survival benefit of post-mastectomy radiotherapy in breast carcinoma patients with T1-2 tumor and 1-3 axillary lymph node(s) metastasis. *Jpn J Clin Oncol* 2012 Jul;42(7):601–8.
- Wang Xueying, Xu Yingying, Guo Shanshan, Zhang Jiabin, Abe Masanobu, Tan Haosheng, et al. T1-2N1M0 triple-negative breast cancer patients from the SEER database showed potential benefit from post-mastectomy radiotherapy. *Oncol Lett* 2020 Jan;19(1):735–44.
- Zhao Jia-Ming, Qi An, Sun Chao-Nan, Li Yu-Bing, Qin Zi-Lan, Guo Hong, et al. Prognostic factors for breast cancer patients with T1-2 tumors and 1-3 positive lymph nodes and the role of postmastectomy radiotherapy in these patients. *Breast Cancer* 2021 Mar;28(2):298–306.
- Luo Chuanxu, Zhong Xiaorong, Fan Yu, Wang Chengshi, Wang Yu, Luo Ting. The effect of postmastectomy radiation therapy on high-risk patients with T1-2N0 breast cancer. *Breast* 2021 Dec;60:1–5.
- Wang Xiaofang, Zhang Li, Zhang Xiaomeng, Luo Jurui, Wang Xuanyi, Chen Xingxing, et al. Impact of clinical-pathological factors on locoregional recurrence in mastectomy patients with T1-2N1 breast cancer: who can omit adjuvant radiotherapy? *Breast Cancer Res Treat* 2021 Nov;190(2):277–86.
- Kunkler IH, Canney P, van Tienhoven G, Russell NS. MRC/EORTC (BIG 2-04) SUPREMO Trial Management Group. Elucidating the role of chest wall irradiation in 'intermediate-risk' breast cancer: the MRC/EORTC SUPREMO trial. *Clin Oncol* 2008 Feb;20(1):31–4.
- Russell NS, Kunkler IH, van Tienhoven G. Determining the indications for post mastectomy radiotherapy: moving from 20th century clinical staging to 21st century biological criteria. *Ann Oncol* 2015 Jun;26(6):1043–4.
- Wilson J Frank, Adam D Currey. Evolving rationale for post-mastectomy radiation. *Breast J* 2018 Jan;24(1):5–6.
- Goodman Chelain R, Brandon-Luke, Seagle L, Kocherginsky Masha, Donnelly Eric D, Shahabi Shohreh, Strauss Jonathan B. 21-Gene recurrence score assay predicts benefit of post-mastectomy radiotherapy in T1-2 N1 breast cancer. *Clin Cancer Res* 2018 Aug 15;24(16):3878–87.
- Kunkler IH, Dixon JM, MacLennan M, Russell NS. European interpretation of North American post mastectomy radiotherapy guideline update. *Eur J Surg Oncol* 2017 Oct;43(10):1805–7.